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[54]发明名称 稳定等渗的冻干蛋白制剂

[57]摘要

本发明描述一种稳定的冻干蛋白质制剂，它可用合适的稀释剂重建成高蛋白质浓度的重建制剂以适用于皮下给药。例如，抗IgE和抗HER2抗体制剂可通过在溶解保护剂存在时对这些抗体冷冻干燥而制得。获得的冻干混合物可重建成高蛋白质浓度的制剂而蛋白质的稳定性没有明显的丧失。

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(54) Title: STABILE ISOTONIC LYOPHILIZED PROTEIN FORMULATION

(57) Abstract

A stable lyophilized protein formulation is described which can be reconstituted with a suitable diluent to generate a high protein concentration reconstituted formulation which is suitable for subcutaneous administration. For example, anti-IgE and anti-HER2 antibody formulations have been prepared by lyophilizing these antibodies in the presence of a lyoprotectant. The lyophilized mixture thus formed is reconstituted to a high protein concentration without apparent loss of stability of the protein.

WHAT IS CLAIMED IS:

1. A stable isotonic reconstituted formulation comprising a protein in an amount of at least about 50 mg/mL and a diluent, which reconstituted formulation has been prepared from a lyophilized mixture of a protein and a lyoprotectant, wherein the protein concentration in the reconstituted formulation is about 2-40 times greater than the protein concentration in the mixture before lyophilization.

2. The formulation of claim 1 wherein the lyoprotectant is sucrose or trechalose.

3. The formulation of claim 1 which further comprises a buffer.

4. The formulation of claim 3 wherein the buffer is histidine or succinate.

5. The formulation of claim 1 which further comprises a surfactant.

6. A stable reconstituted formulation comprising an antibody in an amount of at least about 50 mg/mL and a diluent, which reconstituted formulation has been prepared from a lyophilized mixture of an antibody and a lyoprotectant, wherein the antibody concentration in the reconstituted formulation is about 2-40 times greater than the antibody concentration in the mixture before lyophilization.

7. The formulation of claim 6 wherein the antibody is an anti-IgE antibody or anti-HER2 antibody.

8. The formulation of claim 6 which is isotonic.

9. A method for preparing a stable isotonic reconstituted formulation comprising reconstituting a lyophilized mixture of a protein and a lyoprotectant in a diluent such that the protein concentration in the reconstituted formulation is at least 50 mg/mL, wherein the protein concentration in the reconstituted formulation is about 2-40 times greater than the protein concentration in the mixture before lyophilization.

10. A method for preparing a formulation comprising the steps of:

(a) lyophilizing a mixture of a protein and a lyoprotectant; and

(b) reconstituting the lyophilized mixture of step (a) in a diluent such that the reconstituted formulation is isotonic and stable and has a protein concentration of at least about 50 mg/mL.

11. The method of claim 10 wherein the protein concentration in the reconstituted formulation is from about 80 mg/mL to about 300 mg/mL.

12. The method of claim 10 wherein the protein concentration in the reconstituted formulation is about 2-40 times greater than the protein concentration in the mixture before lyophilization.

13. The method of claim 10 wherein lyophilization is performed at a shelf temperature maintained at about 15-30°C throughout the entire lyophilization process.

14. An article of manufacture comprising:

(a) a container which holds a lyophilized mixture of a protein and a lyoprotectant; and

(b) instructions for reconstituting the lyophilized mixture with a diluent to a protein concentration in the reconstituted formulation of at least about 50 mg/mL.

15. The article of manufacture of claim 14 further comprising a second container which holds a diluent.

16. The article of manufacture of claim 15 wherein the diluent is bacteriostatic water for injection (BWFI) comprising an aromatic alcohol.

17. A formulation comprising a lyophilized mixture of a lyoprotectant and an antibody, wherein the molar ratio of lyoprotectant:antibody is about 100-1500 mole lyoprotectant:1 mole antibody.

18. Use of the formulation of claim 1 in the preparation of a medicament for treating a mammal which has a disorder requiring treatment with the protein in the formulation.

19. Use as in claim 18 wherein the formulation is for subcutaneous administration.

20. A formulation comprising anti-HER2 antibody in amount from about 5-40 mg/mL, sucrose or trehalose in an amount from about 10-100 mM, a buffer and a surfactant.

21. The formulation of claim 20 further comprising a bulking agent.

22. The formulation of claim 20 which is lyophilized and stable at 30°C for at least 6 months.

23. The formulation of claim 20 which is reconstituted with a diluent such that the anti-HER2 antibody concentration in the reconstituted formulation is from about 10-30 mg/mL, wherein the reconstituted formulation is stable at 2-8°C for at least about 30 days.

24. A formulation comprising anti-IgE antibody in amount from about 5-40 mg/mL, sucrose or trehalose in an amount from about 80-300 mM, a buffer and a surfactant.

25. The formulation of claim 24 which is lyophilized and stable at about 30°C for at least 1 year.